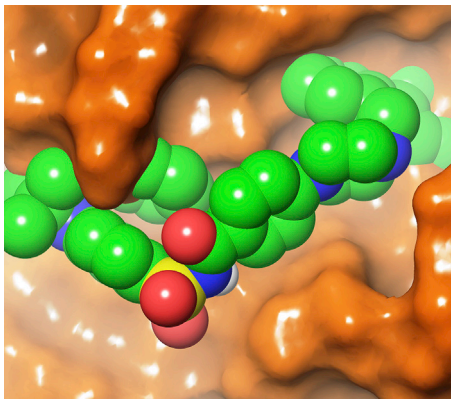
In This Issue

CellPress

Targeting Protein-Protein Interactions: Bring It On!

PAGE 689



Protein-protein interactions (PPIs) mediate numerous biological processes. This makes finding small molecules that target PPIs of high interest. But finding such small molecules continues to be a challenge. Laraia et al. review the specific challenges of developing PPI inhibitors and highlight four innovations they consider critical to overcome these challenges.

Inhibition of AMPK and Insulin Release

PAGE 705

AMP-activated protein kinase (AMPK) is a central regulator of energy metabolism. Therapeutic AMPK inhibition is regarded as a strategy to combat diabetes, cancers, and neurodegeneration. Scott et al. have identified MT47-100 as an AMPK inhibitor acting through an allosteric drug-binding site. These findings will aid development of AMPK-targeting therapeutics.

hRAD51 AND HIV-1: Bosom Bodies or Arch Enemies

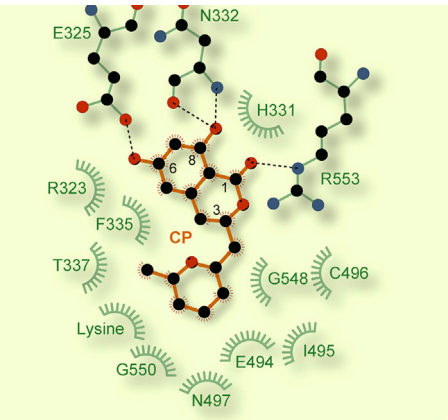
PAGE 712

HIV-1 replication depends on the integration of the viral genome into the infected cell DNA. This step can be modulated by the hRAD51 DNA repair protein. Pharmacological strategies, employed by Thierry et al., establish a direct correlation between the stimulation of hRAD51 and the inhibition of HIV-1 integration highlighting the multiple and opposite regulatory functions of the recombinase on this important replication step.

Pseudoglycosyltransferase VldE

PAGE 724

Abuelizz and Mahmud used OtsA, VldE, and chimeric proteins to study pseudoglycosyltransferase catalysis. They found that the N-terminal domain of VldE is responsible for its distinct substrate specificity and catalytic activity and that the chimeric proteins can produce hybrid pseudo-aminodisaccharides.



Cladosporin's Species Selectivity Explained

PAGE 734

Cladosporin is a potent antimalarial targeting the lysyl-tRNA Synthetase (LysRS), with strict species selectivity. Fang et al. present structural and biochemical analyses of the LysRS-cladosporin complexes, revealing a surprising molecular basis for the species and family selectivity through binding the universal pocket of ATP.

From DNA Fragments to Mechanism of Macrodiolide Formation

PAGE 745

Zhou et al. describe the in vitro cloning from genomic DNA fragments of the intact biosynthetic gene cluster for conglobatin. This provides proof of concept for more convenient recovery of large gene clusters for both known and silent biosynthetic pathways, enabling their detailed analysis.

Hijacking Cereblon to Target BRD4

PAGE 755

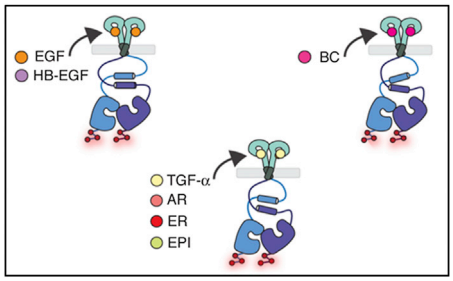
Lu et al. designed a potent BRD4 degrader using the PROTAC technology by recruiting BRD4 to the E3 ligase cereblon. This study demonstrates the potential of hijacking cereblon or other E3 ligases through the PROTAC platform for effectively targeting pathological proteins as a therapeutic approach.

The Science behind Licking a Frog

PAGE 764

Vardy et al. compare the activation of opioid receptors from human and frogs. Deltorphin, an opioid peptide secreted by frogs, was shown to be highly potent in the human DOR but inactive in the frog receptor. Bioinformatics, structural analysis, and extensive mutagenesis revealed that a single amino acid is responsible for the species selectivity exhibited by deltorphin.

A Playful EGFR Juxtamembrane Region



PAGE 776

Doerner et al. report that the EGFR juxtamembrane region assembles into three different anti-parallel coiled coils whose structure both depends on growth factor identity and correlates with downstream signaling. Alternative coiled coils communicate chemical information across the plasma membrane.

Saying "Yes" to Targeting NOS

PAGE 785

Holden et al. report on novel bacterial nitric oxide synthase (bNOS) inhibitors that work synergistically with agents that induce oxidative stress to dramatically inhibit the growth of methicillin resistant *Staphylococcus aureus* (MRSA).

Cobalt(III) Protoporphyrin and miRNA Processing

PAGE 793

miRNA processing defects have been reported in many human diseases including 22q11.2 deletion syndrome. Barr et al. show that Co(III) protoporphyrin activates miRNA processing by binding and activating the RNA-binding protein DGCR8 and compensates processing deficiency in *Dgcr8*$^{+/-}$ mouse neurons.

